Department of Health & Human Services **Public Health Service**

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Therapeutics Research and Review

DATE: May 27, 1999

FROM: Lisa G. Rider, MD, Medical Officer, Division of Monoclonal Antibodies and Adjunct Clinical Reviewer, Division of Clinical Trial Design and Analysis

RE: Supplemental Biological License Application Review for Enbrel (recombinant human tumor necrosis factor receptor Fc fusion protein, rhu TNFR:Fc), BLA no.98-1296 (Initial submission November 24, 1998; IND 5088)

FINAL ACTION DATE: May 27, 1999

THROUGH: William Schwieterman, M.D., Chief, Infectious Disease and Immunology Branch, DCTDA, OTRR, CBER
Karen Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, OTRR, CBER

TO: File (final sign-off ncd 1-6-00)

SUBJECT: Clinical review

TABLE OF CONTENTS:

I. BACKGROUND.

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in children, with an estimated prevalence of 57 - 113 per 100,000 children under the age of 16 in the United States (Singsen 1990). JRA is a group of illnesses characterized by chronic, idiopathic synovitis, with onset prior to 16 years of age. These disorders have been divided into clinically distinct subsets based on the extent of joint involvement and extra-articular manifestations, including the subsets pauci-articular (< 5 joints), poly-articular (≥ 5 joints) and systemic-onset JRA (arthritis with systemic features of fever and rash). Recent long-term follow-up studies have suggested that JRA is not benign, with approximately 30% of patients developing severe functional disability, 31-55% with unremitting synovitis, and 1% dying from their illness (Wallace 1991). Approximately one-third of JRA patients achieve control of their disease with nonsteroidal anti-inflammatory drugs (NSAIDS) and physical and occupational therapy. A large randomized controlled trial in children with polyarticular course JRA whose disease was resistant to NSAIDs and other agents demonstrated efficacy of methotrexate (MTX) compared to placebo, with an acceptable safety profile (Giannini 1992). However, even when MTX is used in adequate doses, some patients fail to respond or respond only partially (Lovell 1997). Poor prognostic factors for JRA include polyarticular disease course, presence of rheumatoid factor (RF), persistent disease activity, poor response to medications, female gender, and delay to treatment (Bowyer, S. FDA JRA Workshop, July 23, 1996; Gare and Fasth 1995, Wallace 1991).

Although the causes of JRA are not known and the mechanism that perpetuates the synovial inflammatory process is not understood clearly, limited evidence implicates tumor necrosis factor (TNF) in the pathogenesis of JRA. Immunohistochemistry studies of synovial tissue demonstrate high levels of TNFα and moderate expression of TNFβ in joint specimens from polyarticular course JRA patients (Grom 1996). TNFα and soluble TNF receptors (p55 and p75) are also increased in the serum and synovial fluid of JRA patients with polyarticular, systemic and pauciarticular onset (Mangge 1995; Lepore 1994; Gattorno 1996). Synovial fluid mononuclear cells producing TNFα and TNFβ were also detected in 37 – 45% of JRA patient samples (Eberhard 1994).

In the document entitled "Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)", the Agency has outlined a policy for drug development for JRA which encourages sponsors licensing products for adult RA to simultaneously obtain dosing and safety data in polyarticular course JRA for inclusion in the dosing and pediatric use sections of the label. For agents in a new pharmacologic class which are not yet approved for adult RA, sponsors desiring a labeled indication for use in JRA are advised to perform full efficacy studies in JRA, which include all subsets of JRA.

In accordance with the Guidance Document and based on discussions with the Agency, Immunex has submitted a two phase study in polyarticular-course JRA patients for review under the BLA, which has included pediatric pK and safety data in 69 patients for 3 months, followed by a randomized withdrawal double-blinded placebo-controlled study in patients who responded to Enbrel in part 1. Pharmacokinetic and safety data were available from 54 patients completing open-label treatment with ENBREL at the time that the adult RA licensure application was filed in the summer of 1998. The current application includes data from the 15 additional patients, as well as the results of the randomized portion of the trial. The application is notable as the first agent to be licensed for JRA in more than a decade and the first biologic product to be licensed for JRA.

Proposed indication by sponsor
ENBREL is indicated for reduction in signs and symptoms of polyarticular-course juvenile rheumatoid arthritis.

II. CLINICAL TRIAL DESIGN AND CONDUCT

A. Study Design.

This was a two-part, multi-center study designed to evaluate the safety, population PK, and efficacy of TNFR:Fc (0.4 mg/kg, maximum 25 mg) in pediatric patients with polyarticular course, active JRA who were refractory or intolerant to MTX. Disease onset could have been systemic, polyarticular, or pauciarticular; however, patients who had systemic onset disease could not have systemic symptoms at enrollment. In Part 1 of the nine site multi-center study, 69 patients ages 4 – 17 years of age received open-label TNFR:Fc at a dose of 0.4 mg/kg (maximum 25 mg/dose) SC twice weekly for 90 days. Responses were assessed at baseline and days 15, 30, 60 and 90, using the JRA Definition of Improvement (DOI) [Giannini, 1997]. Patients were permitted to remain on a stable dose of a single NSAID and/or corticosteroid at a dose of ≤ 0.2 mg/kg or 10 mg maximum. To be considered a responder, patients had to demonstrate a response at day 90 as defined by the JRA DOI, which includes ≥ 30% improvement in at least three of the six following criteria, with ≥ 30% worsening in not more than one of the six assessments: physician's global assessment, patient/parent global assessment, number of active joints (swelling not due to deformity or joints with LOM plus pain and/or tenderness), number of joints with LOM (modified by sponsor to include LOM plus pain and/or tenderness), functional assessment (Childhood Health Assessment Questionnaire [CHAQ] (Singh 1994), and ESR (Giannini, 1997). Additional response assessments included articular severity score, pain score, duration of morning stiffness and C-reactive protein (CRP). Trained joint assessors who were not involved in the patient's clinical are and who were blinded to study treatment in part 2 of the study, performed the joint assessments, whereas hysician global assessments were performed by the principal investigators.

At the end of the 90 days, patients with disease response as defined by the JRA DOI were randomized to Part 2 of the study, the double blind, efficacy portion. Randomized patients received placebo or continued administration of TNFR:Fc at a dose of 0.4 mg/kg until either disease flare occurred or 4 months elapsed, whichever was earlier. The primary efficacy endpoint of the trial was the proportion of patients developing a disease flare in the two study arms. Disease flare (a significant worsening of disease activity compared to Day 90) was defined as ≥ 30% worsening in three of the six JRA Core Set Criteria and ≥ 30% improvement in not more than one of the six JRA Core Set Criteria, with a minimum of two active joints (swollen or LOM + P/T). If global assessments were used to establish flare, they had to have worsened by at least two units. The definition of flare was developed from a sensitivity analysis of several definitions of flare using data from the placebo-controlled trial of MTX in JRA (Giannini 1992), and was also accepted by the investigators and FDA as a definition with face validity. Secondary endpoints for the randomized portion of the study included time to flare and responses to Enbrel, defined by the JRA DOI.

The dose of Enbrel used in the JRA study of 0.4 mg/kg or a maximum dose of 25 mg administered subcutaneous twice weekly was based on a phase II study in adult RA. In this study, 16.0 mg/m^2 demonstrated maximal efficacy, which was converted to a 25 mg fixed dose.

The study specified the following inclusion criteria:

- Between 4 and 17 years of age.
  Diagnosis of JRA by ACR criteria (Cassidy 1986). Disease onset may have been systemic, polyarticular, or pauciarticular, but disease course is polyarticular.

- At time of screening, must have had continuing active disease defined as ≥ 5 swollen joints and ≥ 3 joints with LOM + P/T (minimum of five active joints).
- Disease must have been refractory to MTX or patient must have been intolerant of MTX (physician defined).
- No treatment with DMARDs, intravenous immunoglobulin, cytotoxic agents or intra-articular steroids within 28 days before receipt of study drug. No treatment with MTX at least 14 days before dosing with study drug.
- Prepubescent and not expected to reach puberty for at least 8 months, or practicing adequate contraception if postpubertal and sexually active; not pregnant.
- Stable hematocrit of ≥ 24%.

The trial excluded subjects who had:

Functional Class IV by ACR criteria

- Clinically significant deviations from normal values for any of the following laboratory parameters: Platelet count < 100,000 cells/cmm; total white cell count < 4000 cells/cmm; neutrophils < 1000 cells/cmm; hepatic transaminase levels > 2 times upper limit of normal (ULN); bilirubin > 2 times ULN; and creatinine clearance < 90 mL/min/1.73 smm BSA or a GFR of < 90 mL/min/1.73 smm BSA.
- Positive tests for HIV, HBsAg, or hepatitis C antibody, or anti-dsDNA
- Participation in an investigational drug or biologic study within past 3 months.
- History of current psychiatric illness; history of alcohol or drug abuse.
- Any concurrent medical condition which would, in the Investigator's opinion, compromise the patient's ability to tolerate the study drug or comply with the protocol.

. Study conduct

ENBREL was supplied as a sterile lyophilized powder in vials containing 25 mg ENBREL is TRIS-buffered solution with mannitol and sucrose. Placebo was supplied as a sterile lyophilized powder in vials containing the same buffered solution. Vials were shipped from Immunex to the clinical sites and were stored refrigerated in the pharmacy.

For part 2 of the study, subjects were randomized at day 90 to placebo or ENBREL according to a computer-generated randomization schedule with blocked randomization using a fixed block size of two. The block size was also inverted for the "few" vs. "many" joint stratification list at each study site. Randomization was stratified according to study site as well as to active joint count (0 – 2 joints vs. ≥ 3 active joints at day 90). Patients in the ENBREL arm and placebo arm were both randomized at a median of 92 days. Four stratification errors were made in the randomization: 3 patients with low joint counts (0 – 2) were erroneously stratified to the many (≥ 3) joint count list (Patients # ———— and 1 patient with many joints was erroneously stratified to the few joint count list (Patient # —— Two of these errors related to the study site reporting baseline joint counts, rather than day 90 joint counts, and two stratification errors were due to Immunex Logistics using the incorrect randomization list. Further discussion of this topic is provided by the statistical reviewer.

Protocol deviations and compliance.

Four patients did not meet the inclusion criteria of ≥ 3 joints with LOM and pain or tenderness at baseline (day 0) examination (patient #s ———— Additional patients did not meet this criteria at screening, but did at the baseline examination. All were enrolled in part 1, and patients ———— were also randomized in art 2, but only patient —— was specifically not allowed to continue to part 2 due to not meeting entry criteria for LOM. Four patients who responded in part 1 violated protocol in receiving prednisone at ≥ 0.4 mg/kg in

part 1 (patients # ——————— Only patient # — was declared a non-responder in part 1 and not allowed to enroll in part 2 due to protocol violation; however the other patients should not have enrolled in part 2 as well. One part 1 non-responder received an intra-articular glucocorticoid injection for a Baker's cyst.

Several patients had insufficient withdrawal times from MTX and other DMARDs: Patient # — had a 13 day washout period for MTX, instead of 14 days as required by the protocol. Patients # ——————— had insufficient withdrawal time from DMARDs (19 – 24 days, instead of 28 days), in some cases resulting in patients being randomized before, rather than after other patients, as would have occurred with the proper length of DMARD withdrawal. Sensitivity analyses omitting these protocol violators were performed and are provided later in the review.

Two patients who had anti-dsDNA autoantibodies at screening were assigned a patient number, but received no doses of medication and were not included in the study. Seven patients (10%) missed one dose of TNFR:Fc, six because of subject error and one due to withholding for an adverse event. One patient (1.4%) missed two doses of medication and then withdrew from study.

C. Patient Population.

Patient disposition.

A total of 69 patients received Enbrel in a three-month open label study, and 64 patients completed 12 weeks of dosing. The majority of subjects who did not enter part 2 had lack of response to ENBREL in part 1. The other reasons for subjects discontinuing study medication before 12 weeks include lack of response, patient/parent refusal, and one adverse event (one patient developed urticaria after the first dose of TNFR:Fc and withdrew at that time). One patient was not allowed to enter part 2 due to violation of study entry criteria. Fifty-one patients entered part 2 of the study; 26 were randomized to placebo and 25 to ENBREL. All patient dropouts in part 2 of the study were related to the development of disease flare, as specified in the definition of disease flare. However, three patients did not drop out immediately upon meeting criteria for a disease flare and remained on placebo for < 1 month after meeting flare criteria and three patients remained on ENBREL 4 - 45 days after meeting flare criteria.

Table 1: PATIENT DISPOSITION

Patients entered 69		
Part 1, Enbrel 0.4 mg/kg (n = 69)	**Part 2, Placebo (n = 26)**	**Part 2, Enbrel 0.4 mg/kg (n = 25)**
Completed 12 weeks dosing 64 (93%)	Completed 12 weeks dosing 7 (27%)	Completed 12 weeks dosing 19 (76%)
• Adverse event: **1** • Patient/parent refusal: **2** • Nonresponder in part 1: early dropout: **2** • Protocol violations: **3*** • Nonresponder in part 2: day 90 dropout: **12**	• Patient/parent refusal: **1** • Response status: flared **18**	• Response status: flared: **6**

* Immunex declared three patients as violating protocol (2 for < 3 joints with LOM + P/T at entry and 1 for receiving a burst of prednisone during part 1) and therefore completing part 1, but not permitted to go on to part 2. Actually, 4 patients violated entry criteria for LOM + P/T, 4 patients violated protocol for maximum dose of ticosteroid and/or steroid pulse during study, 5 patients had insufficient withdrawal time from DMARDs or TX.

The demographics of the study subjects are given in Table 2 and baseline arthritis activity measures are given in Table 2.

Table 2: Demographic Characteristics and Disease History

	- Part 1 -	Part 2		
Characteristic	TNFR:Fc (N = 69)	Total (N = 51)	Placebo (n = 26)	TNFR:Fc (n = 25)
Mean age (years)	10.5	10.6	**12.2**[1]	**8.9**[1]
Age Group (n [%])				
4 – 8	25 (36)	18 (35)	5 (19)	13 (52)
9 – 12	14 (20)	9 (18)	4 (15)	5 (20)
13 - 17	30 (43)	24 (47)	17 (65)	7 (28)
Sex (n [%])				
Female	43 (62)	34 (67)	15 (58)	19 (76)
Male	26 (38)	17 (33)	11 (42)	6 (24)
Race (n [%])				
Caucasian	52 (75)	37 (73)	**23 (88)**[2]	**14 (56)**[2]
Hispanic	9 (13)	8 (16)	2 (8)	6 (24)
Black	6 (9)	4 (8)	1 (4)	3 (12)
Other	2 (3)	2 (4)	0	2 (8)
Mean height (cm)	135	136	144	128
Mean weight (kg)	36	38	**43**[3]	**34**[3]
Mean Body Surface Area (m^2)	1.07		**1.29**[3]	**0.95**[3]
Mean JRA duration (years)	5.9	5.8	6.4	5.3
JRA onset type (n [%])				
Pauciarticular	7 (10)	3 (6)	1 (4)	2 (8)
Polyarticular	40 (58)	31 (61)	17 (65)	14 (56)
Systemic	22 (32)	17 (33)	8 (31)	9 (36)
RF Positive (n [%])	15 (22)	12 (24)	8 (31)	4 (16)
Previous MTX (n [%])	69 (100)	51 (100)	26 (100)	25 (100)
Nonresponsive	58 (84)	42 (82)	22 (85)	20 (80)
Intolerant	15 (22)	12 (24)	5 (19)	7 (28)
DMARDs (any) at washout (n [%])	51 (74)	35 (69)	19 (73)	16 (64)
MTX	50 (72)	34 (67)	18 (69)	16 (64)
Hydroxychloroquine	13 (19)	9 (18)	7 (27)	2 (8)
Concomitant therapy at start of washout period (n [%])				
Corticosteroids	25 (36)	19 (37)	13 (50)	6 (24)
NSAIDs	66 (96)	49 (96)	24 (92)	25 (100)
Mean daily steroid dose (mg/day)	5.6	5.8	5.5	6.5

Nominal P values, not corrected for multiple comparisons: [1]P = 0.0026, [2]P = 0.022, [3]P = 0.026

Regarding part 1 of the study, all three onset courses were represented, although polyarticular onset was most mmon. Twenty-two percent were rheumatoid factor (RF) positive, which is higher than 1% RF positive observed in a large US registry of new-onset patients (Bowyer and Roettcher, 1996).

Table 3: Disease Activity Measures for Part 1 and Part 2 (Median Values)

Parameter	Part 1 (n=69)	Part 2 Placebo (n=26) Day 90	Part 2 TNFR:Fc (n = 25) Day 90
JRA Core Set Criteria			
Total active joints[a]	28	7.5	13.0
Joints with LOM + P/T[b]	10	1.0	2.0
Physician global assessment[c]	7	1	2
Patient/parent global assessment[c]	5	1	2
CHAQ[d]	1.4	0.4	0.9
ESR[e]	35	12	15
Additional Assessments			
Articular severity score[f]	88	36	35
Duration of stiffness (min.)	45	5	15
Pain (VAS)[c]	3.6	0.3	1.3
CRP[g]	3.5	0.3	0.2
Other			
Swollen joints[h]	25	6.0	12.0
Joints with LOM[b]	23	17	12

a. Score of 0 – 73. b. Score of 0 - 71.
c. 0 = best; 10 = worst. d. 0 = best; 3 = worst.
e. Normal range: 1 - 30 mm/hr for females; 1 – 13 for males.
f. Score of 0 – 962. g. Normal range: 0 - 0.79 mg/dL.
h. Score of 0 – 66.

Although girls were in majority, the female: male ratio of 1.65 was not as great as usually seen in polyarticular JRA, and more patients of ethnic minority groups were enrolled than have been observed in a national JRA registry (Bowyer and Roettcher, 1996). The 69 children had disease for an average of 5.9 years and all had received MTX in the past; 84% had disease refractory to MTX and 22% were intolerant of MTX. They had received an average of 2.4 DMARDs (including cytotoxic agents and intravenous gammaglobulin) prior to study entry. Twenty-four percent had received experimental therapy. They had a median of 28 active joints at study entry. In summary, the patient population in part 1 of the study included patients with polyarticular-course JRA with a number of poor prognostic factors whose disease activity was more severe than an average university clinic population of JRA patients and which was as severe as the adult RA patients enrolled in phase 3 studies of ENBREL.

Regarding part 2 of the study, which included 51 patients all of whom had demonstrated a clinical response to ENBREL in twelve weeks of open-label treatment, patients in the ENBREL-treatment arm were younger (with a lower mean weight and body surface area) and had fewer Caucasian patients than the placebo arm (Table 2). Other demographic characteristics and disease activity measures at day 90, the date of randomization, were balanced between arms (Tables 2,3), although patients in the ENBREL arm had a higher active joint count at day 90 than placebo patients. The demographic imbalances between arms, coupled with errors in stratification, were the rationale for the statistical reviewer to examine the possibility of selection bias in part 2 of the study.

III. EFFICACY ANALYSIS AND RESPONSE TO THERAPY.

A. Primary endpoint.

Results of analyses of the primary and secondary endpoints from part 2 of the study are summarized in Table 4.

Table 4: Primary and secondary endpoint in Part 2:
Proportion of subjects meeting JRA Defn of Flare Criteria and Time to Flare

	Placebo (N = 26) n (%)	Enbrel (N = 25) n (%)
JRA Flare 30%	20 (77)*	6 (24)*
Time to Flare	29 days**	≥ 116 days**
JRA Flare 30% by Onset Subtype		
Pauciarticular	1/ 1 (100)	0/ 2 (0)
Polyarticular	13/17 (76)	2/14 (14)
Systemic	6/ 8 (75)	4/ 9 (44)

* P = 0.0073 ** P = 0.0001

A statistically significant increase in the proportion of subjects who developed a disease flare, based on the JRA Definition of Flare, was observed in subjects receiving placebo compared to subjects receiving ENBREL 0.4 mg/kg in part 2 of the study. Patients receiving placebo also had a significantly shorter time to disease flare than patients receiving ENBREL. There was no statistically different rate of disease flare in pauciarticular- or systemic-onset JRA compared to polyarticular-onset, although systemic-onset JRA patients who remained on ENBREL were more likely to flare than patients in the other disease onset subsets.

B. Corroborating analyses.

The results of the sponsor's analysis of the individual components of the JRA Core Set, as well as other disease activity measures, are summarized in Table 5. Last Observation Carried Forward was used for the timepoints after subjects discontinued study medication. Subjects treated with ENBREL demonstrated improvement in all disease activity measures, whereas subjects receiving placebo had worsening in all components of the core set. Subjects treated with ENBREL exhibited a statistically significant improvement in each disease activity measure compared to subjects receiving placebo. Of note, objective measures including ESR and CRP increased on placebo similarly to other disease activity assessment parameters, whereas for patients remaining on ENBREL, ESR and CRP responded similarly to other disease activity assessment parameters.

Table 5: Disease Activity Measures at Days 90 and 210 (Median Values) for Responders at Month 3 who were Randomized to Part 2 of the Study

		Placebo (n = 26)		Enbrel (n = 25)		
Parameter	Day 90	Day 210*	Day 210 – Day 90 Median Change	Day 90	Day 210*	Day 210 – Day 90 Median Change
JRA Core Set Criteria						
Total active joints[a]	7.5	13.0	7.5	13.0	7.0	-2
Joints with LOM + P/T[b]	1.0	4.5	3	2.0	1.0	0
Physician global assessment[c]	1	5	2.5	2	2	0
Patient/parent global assessment[c]	1	5	3	2	3	0
CHAQ[d]	0.4	1.2	0.5	0.9	0.8	-0.25
ESR[e]	12	30	11.5	15	18	0
Additional Assessments						

Articular severity score[f]	36	66	24.5	35	38	-7
Duration of stiffness (min.)	5	38	30	15	5	-5
Pain (VAS)[c]	0.3	3.5	2.1	1.3	1.5	0
CRP[g]	0.3	3.0	1.7	0.2	0.4	0
Other						
Swollen joints[h]	6.0	11.0	4.5	12.0	4.0	-2
Joints with LOM[b]	17	22	5	12	9	-2

a. Score of 0 – 73. b. Score of 0 - 71. c. 0 = best; 10 = worst.
d. 0 = best; 3 = worst.. e. Normal range: 1 - 30 mm/hr for females; 1 - 13 for males.
h. f. Score of 0 – 962. g. Normal range: 0 - 0.79 mg/dL. h. Score of 0 – 66.

- * For patients who met criteria for flare and dropped out of the study early, last observation carried forward analysis was used.
- Nominal P values not corrected for multiple comparisons: $P < 0.01$ for placebo vs. Enbrel Day 210 - Day 90 Median percent change, except for CRP, $P = 0.02$

Responses to ENBREL vs. placebo were also examined using the JRA DOI.

Table 6: Responses to Therapy in Part 2 for Patients who had a clinical response in Part 1 and were randomized to Part 2:

30%, 50%, and 70% Response Rates at Day 210

	Number (%) Patients – Day 210 vs. Day 90	
Response Criteria	Placebo (n = 26)	TNFR:Fc (n = 25)
JRA DOI 30%	1 (4)[1]	10 (40)[1]
JRA DOI 50%	1 (4)	5 (25)
JRA DOI 70%	1 (4)	2 (4)

[1] = 0.002

The FDA performed additional analyses of the clinical responses in Part 2, using the Smirnov test (Table 7), which assesses the difference between the level of clinical response attained from Day 210 to Day 90, the date of randomization. The results were significant that patients remaining on ENBREL demonstrated additional clinical response from Day 90, whereas patients receiving placebo did not.

Table 7: FDA Analysis of Clinical Responses to Therapy in Part 2, for patients who responded in part 1 and were randomized to Part 2, by Smirnov Test

	No JRA DOI n (%)	JRA DOI 30 – 50% n (%)	JRA DOI 50 – 70% n (%)	JRA DOI > 70% n (%)	Total n
Placebo	17 (65%)	3 (12%)	1 (4%)	5 (19%)	26
ENBREL	5 (20%)	2 (8%)	7 (28%)	11 (44%)	25

P = 0.0008, Two Sided Exact conditional Smirnov test

Durability of Response:

The proportion of subjects attaining a durable clinical response which, once present, persisted through month 6, was assessed. This could only be assessed in patients who completed 6 months of therapy and, therefore responded at day 90 and were randomized to part 2 of the study. As shown in Table 8, an increased proportion subjects in the ENBREL arm attained a durable JRA DOI response compared to subjects receiving placebo. atients achieved durable responses beginning at 30 days, and an increasing proportion of durable responders

was observed out to month 6. The median time to a durable response was 61 days for the 25 subjects who received ENBREL throughout the study.

ble 8: Cumulative Percent of Patients Achieving a 30% DOI Response Persisting through Month 6

..udy Day	Placebo (n = 26)*	Enbrel (n = 25)
Part 1		
15	8	16
30	12	40
60	15	48
90	15	64
Part 2		
120	15	68
150	15	68
180	15	79
210	15	79

* Patients received Enbrel in part 1 of the study and placebo in part 2.
P < 0.026 beginning at day 30.

C. Subset analyses for the primary efficacy endpoint.
To assess the influence of baseline disease activity and demographic variables on the results of the study, the sponsor performed logistic regression analyses. Of note, age, weight, body surface area, and race, variables which were imbalanced between placebo and ENBREL arms, were not predictive of the subject's likelihood of developing a disease flare (Tables 11 – 13, 17). In contrast, higher baseline and day 90ESR, as well as baseline CRP, physician and patient/parent global assessments were associated with disease flare in univariate logistic ression analyses (Table 9).

Regarding ESR, within each treatment group, the differences in ESRs were significant: The median ESR in the arm remaining on ENBREL was 82 mm/hr for 6 patients who developed a disease flare, vs. 12 mm/hr for 19 patients who did not develop a disease flare in part 2 (P = 0.009 by Wilcoxon Rank Sum test). For patients receiving placebo in part 2, the median ESR was 36 mm/hr in the 20 patients developing a disease flare vs. 13 mm/hr in the 6 placebo patients who did not flare (P = 0.024).

Results of Univariate Subset Analyses:
Table 9: Univariate Logistic Regression Analyses for Predictors of Flare in Part 2:

- **Variables which were associated with flare:**
  -Baseline ESR (Odds Ratio [OR] = 1.9, P = 0.002)
  -Baseline CRP (OR = 1.2, P = 0.008)
  -Baseline MD global assessment (OR = 2.2, P = 0.003)
  -Baseline patient/parent global assessment (OR = 1.6, P = 0.006)
  -Day 90 ESR (OR = 1.04, P = 0.042)
- **Variables which were not predictive of flare at Day 210:**
  - Baseline (OR = 1.02, P = 0.55) and 90 day active joint count (OR =0.98, P = 0.66)
  - Baseline (OR = 1.01, P = 0.14) and 90 day articular severity score (OR = 1.0, P > 0.5)
  - Baseline (OR = 2.06, P = 0.11) and 90 day CHAQ (OR = 1.2, P = 0.66)
  - Baseline LOM + P/T (OR = 1.06, P = 0.08)
  - 90 day MD global assessment (OR = 1.06, P = 0.74)
  - 90 day patient/parent global assessment (OR = 1.2, P = 0.35)
  - 90 day CRP (OR = 1.09, P = 0.16)

Additional parameters which were not predictive of disease flare are shown in Tables 10 – 19:

Table 10: Flare rates (Day 210 – Day 90) by JRA onset type

	JRA Definition of Flare	
Onset Subset	Placebo, n (%)	ENBREL, n (%)
Pauciarticular onset	1/ 1 (100)	0/ 2 (0)
Polyarticular onset	13/17 (76)	2/14 (14)
Systemic onset	6/ 8 (75)	4/ 9 (44)

P = 0.32 by Breslow Day test.

Table 11: Flare rates by Age

	JRA Definition of Flare	
Age (years)	Placebo, n (%)	ENBREL, n (%)
4 – 8	3/ 5 (60)	2/13 (15)
> 8 – 12	4/ 4 (100)	1/ 5 (20)
> 12 – 17	13/17 (76)	3/ 7 (43)

P = 0.40 by Breslow Day test. Logistic Regression Analysis: Odds Ratio = 1.1, P = 0.27

Table 12: Flare rates by Weight

	JRA Definition of Flare	
Weight (kg)	Placebo, n (%)	ENBREL, n (%)
< 30	5/ 7 (71)	3/14 (21)
30 – 39	6/ 6 (100)	0/ 4 (0)
≥ 40	9/13 (69)	3/ 7 (43)

= 0.10 by Breslow Day test. Logistic Regression Analysis: Odds Ratio = 1.01, P = 0.47

Table 13: Flare rates by Body Surface Area

	JRA Definition of Flare	
Body Surface Area (m^2)	Placebo, n (%)	ENBREL, n (%)
< 0.9	2/ 4 (71)	2/10 (20)
< 1.2	6/ 6 (100)	1/ 8 (13)
≥ 1.2	12/16 (75)	3/ 7 (43)

P = 0.16 by Breslow Day test. Logistic Regression Analysis: Odds Ratio = 1.74, P =0.49

Table 14: Flare rates by Gender

	JRA Definition of Flare	
Gender	Placebo, n (%)	ENBREL, n (%)
Female	14/15 (93)	4/19 (21)
Male	6/ 11 (55)	2/ 6 (33)

P = 0.041 by Breslow Day test. Logistic Regression Analysis: Odds Ratio = 2.8, P =0.18

Table 15: Flare rates by Study Site:

	JRA Definition of Flare	
Study Site Number	Placebo, n (%)	ENBREL, n (%)
31	4/ 4 (100)	1/ 4 (25)
174		0/ 1 (0)
182	1/ 2 (50)	0/ 2 (0)
42	2/ 2 (100)	1/ 2 (50)
502	1/ 2 (50)	1/ 1 (100)

503	7/ 7 (100)	3/ 7 (43)
504	2/ 4 (50)	0/ 3 (0)
506	1/ 1 (100)	0/ 1 (0)
4	2/ 4 (50)	0/ 4 (0)

= 0.64 by Breslow Day test.

Table 16: Flare rates by Baseline Rheumatoid Factor status.

	JRA Definition of Flare	
Rheumatoid Factor	**Placebo, n (%)**	**ENBREL, n (%)**
Positive	8/ 8 (100)	0/ 4 (0)
Negative	12/18 (67)	6/21 (29)

P = 0.034 by Breslow Day test. Logistic Regression Analysis Odds Ratio = 1.0, P = 0.49

Table 17: Flare rates by Race

	JRA Definition of Flare	
Race	**Placebo, n (%)**	**ENBREL, n (%)**
Caucasian	17/23 (74)	3/14 (21)
Non-Caucasian	3/ 3 (100)	3/11 (27)

P = 0.41 by Breslow Day test.

Table 18: Flare rates by Disease Duration

	JRA Definition of Flare	
Disease duration (years)	**Placebo, n (%)**	**ENBREL, n (%)**
< 5	7/10 (70)	4/13 (31)
5	13/16 (81)	2/12 (17)

= 0.29 by Breslow Day test. Logistic Regression Analysis Odds Ratio = 0.95, P = 0.90

Table 19: Flare rates by Baseline Corticosteroid Use

	JRA Definition of Flare	
Corticosteroid Use at Baseline	**Placebo, n (%)**	**ENBREL, n (%)**
Yes	11/13 (85)	3/ 6 (50)
No	9/13 (69)	3/19 (16)

P = 0.58 by Breslow Day test.

Because of the multiple variables associated with disease flare in the univariate analysis, a backwards logistic regression analysis was performed by the sponsor to determine the interaction between variables in a multivariate analysis (Table 20). In a model that did not include treatment, baseline ESR was the only factor that remained in the model and was associated with increased risk of disease flare. Being female also increased the risk of having a disease flare, but not significantly. When treatment effect was added into the model, as expected, this was highly significant, with disease flare rate significantly higher in the placebo group than the group remaining on ENBREL therapy in part 2. Baseline ESR remained significantly associated with disease flare in this model.

Table 20: Summary of Backward Regression Analysis of Flare for Part 2

Variable Removed	Chi-Square P Value	Odds Ratio
Baseline ESR	0.031	1.03
nder	0.81	1.16
ıseline CRP	0.85	
Day 90 ESR	0.40	
Baseline MD global assessment	0.40	
Baseline patient/parent global assessment	0.31	
Baseline CHAQ	0.18	
Adding Treatment to model:		
Baseline ESR	0.0027	1.14
Gender	0.166	4.3
Treatment group	0.0006	0.0000

When gender and baseline ESR were included in separate models of the two treatment groups (placebo and ENBREL), girls were more likely to flare than boys in the placebo group, but not in the ENBREL group, but the results were not significant (OR = 10.3, but P = 0.07 for placebo, OR = 0.008, P = 0.81 for ENBREL). Higher baseline ESR was associated with higher likelihood of disease flare in the ENBREL group, but not the placebo arm (OR = 3.9, P = 0.69 for ENBREL, OR = 1.08, P = 0.11 for placebo), although not significantly. In addition, the validity of the logistic regression model in the ENBREL group was questionable, likely resulting from an inadequate number of data points. Overall, the results of the univariate and multiple logistic regression analyses suggest that a higher baseline ESR is associated with a higher likelihood of disease flare, for both ENBREL and placebo-treated patients. Girls may be more likely to flare than boys, although this effect was stronger in the placebo arm and therefore has limited extrapolation to a clinical setting.

ר. Other analyses.

nsitivity analysis.

To assess the sensitivity of the results to protocol violation, two analyses were performed (Table 21). First, the 11 protocol violators who had a response to ENBREL in part 1 and were randomized in part 2, were excluded from the analysis of the primary endpoint, the JRA Definition of Flare. Second, these 11 protocol violators were recategorized as "no flare" for the placebo group and as a "flare" for the ENBREL group. Both analyses demonstrated that there were still more flares in the placebo arm than the ENBREL arm of the study.

Table 21: Sensitivity analysis of protocol violators: JRA Flare 30%

	Placebo	ENBREL
Exclude all protocol violators	16/21 (76%)	4/20 (20%)
P value	P < 0.001 for ENBREL vs. placebo	
Recategorize flares as no flare for placebo group, and no flare as flare for ENBREL group	16/26 (61%)	7/25 (28%)
P value	P = 0.034 for ENBREL vs. placebo	

Because of the potential for unmasking of study subjects in the randomized portion of the trial, particularly with a three month open-label run-in period on ENBREL, several analyses were performed to address this. First, as noted in Table 5, objective measures such as ESR and CRP improved in patients receiving ENBREL to a similar degree as other JRA core set and disease activity measures, whereas for patients receiving placebo, ESR and CRP worsened to a similar degree as other parameters. In a more detailed analysis, a similar proportion of ˋatients in both arms demonstrated improvement in ESR and CRP in part 1 of the study (open-label). In the ındomized portion of the study, a larger proportion of patients in the placebo group than in the group receiving ENBREL, had a ≥ 30% increase in ESR and CRP.

Table 22: Change in ESR and CRP in Placebo vs. ENBREL groups

Parameter	Placebo, (n = 26)* N (%)	Enbrel, (n = 25) N (%)
SR, Part 1		
30% decrease, baseline to day 90	19 (73)	22 (88)
ESR, Part 2		
≥ 30% increase, day 90 to d 210	20 (80)[1]	9 (36)[1]
CRP, Part 1		
≥ 30% decrease, baseline to day 90	18 (69)	19 (76)
CRP, Part 2		
≥ 30% increase, day 90 to day 210	19 (76)[2]	9 (36)[2]

* N = 25 for part 2; [1] P = 0.004, [2] P = 0.01

If unmasking had occurred in the randomized portion of the trial, patients with unmasking side effects, including infections, headache and gastrointestinal intolerance, may have experienced more disease flares than patients without these adverse events. As shown in Table 23, patients with unmasking side effects experienced similar incidences of flare as patients in each arm without these adverse events, further suggesting that the trial was not unmasked.

Table 23: Unmasking adverse events in Part 2 (randomized portion) of the study in placebo and ENBREL arms.

	Flare Rate	
Parameter	Placebo (n = 26) N (%)	ENBREL (N = 25) N (%)
No infection, part 2	15/17 (88)[1]	4/10 (40)[2]
Infection, part 2	5/ 9 (56)[1]	2/15 (13)[2]
No headache or gastrointestinal event, part 2	3/ 4 (75)[3]	4/ 4 (50)[4]
Headache or gastrointestinal event, part 2	15/22 (68)[3]	2/17 (12)[4]

Nominal p values: not corrected for multiple comparisons:
[1] P = 0.14, [2] P = 0.15, [3] P = 1.0, [4] P = 0.059

To further evaluate the possibility of unmasking in the randomized portion of the study, dropouts from each arm were examined. First, patient dropout did not differ across groups, all patients who met criteria for flare dropped out of both arms. Three patients remained on placebo for < 1 month after meeting flare criteria, and three patients remained on ENBREL 4 - 45 days after meeting flare criteria. These patients remained on treatment beyond meeting flare criteria because either the physician or parent/patient did not appreciate a clinical flare at the time that flare criteria were met; in one case, intercurrent illness made it difficult to evaluate the flare. In all analyses, however, the disease activity measures and time points were used from the date flare criteria were met. The 19 patients who dropped out of placebo arm and 6 who dropped out of the ENBREL arm differed across treatment arms in only a few demographic and disease activity characteristics (Tables 24,25). Patients dropping out of the placebo arm were more likely to be Caucasian than ENBREL dropouts. Dropouts from the ENBREL arm had higher ESR, CRP, physician and parent/patient global assessments, and pain scores at baseline than placebo dropouts, but not at day 90 (the point of randomization) or the termination date.

Table 24:

Median Values and P-values for Demographic Characteristics at Baseline for 19 Placebo and Six ENBREL Discontinuations in Part 2

Variable	Placebo	ENBREL	p-value[a]
Age (years)	13	12	0.45
Females (n [%])	13 (68)	4 (67)	1.0
Caucasian (n [%])	**19 (100)**	**3 (50)**	**0.009**
Height (cm)	146	145	0.82
Weight (kg)	38	45	0.97
Duration of JRA (years)	6.7	2.9	0.12
JRA onset type (n [%])			0.26
Pauciarticular	1 (6)	0	
Polyarticular	13 (68)	2 (33)	
Systemic	5 (26)	4 (67)	
Rheumatoid factor positive	7 (37)	0	0.14
Corticosteroid use (n [%])	11 (58)	3 (50)	1.0
NSAID use (n [%])	18 (95)	6 (100)	1.0
Body surface area (m^2)	1.2	1.4	0.97

a. P-values from Wilcoxon rank-sum test (continuous variables) or Fisher's exact test (categorical variables). Tests are two-tailed.

ble 25:

Median Values and P-values for Disease Activity Measures at Baseline and Days 90 and Date of Termination for 19 Placebo and Six ENBREL Discontinuations in Part 2

	Median Values Baseline			Median Values Day 90			Median Values Day 210		
Variable	Placebo	ENBREL	p-value[a]	Placebo	ENBREL	p-value[a]	Placebo	ENBREL	p-value[a]
JRA Core Set Criteria									
Total active joints	28.0	25.5	0.90	8.0	7.0	0.34	16.0	16.5	0.41
Joints with LOM + P/T	10.0	15.5	0.75	1.0	0	0.074	6.5	8.5	0.85
Physician global assessment	**6**	**9**	**0.013**	2	2	0.75	7	8	0.95
Patient/parent global assessment	**5**	**9**	**0.032**	2	1	0.79	6	6	1.0
CHAQ	1.4	2.4	0.12	0.5	0.7	0.77	1.5	1.8	0.57
ESR	**32**	**92**	**< 0.001**	20	18	0.70	33	82	0.15
Additional Assessments									
Articular severity score	88	137	0.59	39	30	0.45	79	117	0.80
Duration of stiffness (min.)	60	270	0.058	5	10	0.53	90	135	0.82
Pain (VAS)	**3.6**	**6.0**	**0.036**	0.2	1.1	0.82	4.9	4.2	0.52
CRP	**3.3**	**14.0**	**0.007**	0.6	1.2	0.87	3.5	14.0	0.080
Other									
Swollen joints	25.0	22.5	1.0	6.0	7.0	0.39	12.0	8.0	0.42
Joints with LOM	25	27	1.0	17	14	0.63	22	29	0.97

v[illegible]s from Wilcoxon rank-sum test.